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10/594,876	09/29/2006	Hannsjorg Sinn	14836-56813	3262

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MORRIS MANNING MARTIN LLP
3343 PEACHTREE ROAD, NE
1600 ATLANTA FINANCIAL CENTER
ATLANTA, GA 30326

EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

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12/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,876	SINN, HANNSJORG	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10,12-15 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10,12-15 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The declaration filed November 3, 2008 is approved.

2. The abstract of the disclosure is objected to because it is insufficiently detailed with respect to the claimed method of preparing the conjugate. Further, legal terminology present in the abstract, i.e. "said", must be omitted. Correction is required. See MPEP § 608.01(b).

3. The claim amendment is not in compliance with 37 CFR 1.121(c)(2), because at claim 3, line 3, "(GVHD)" has been inserted at the end of the line but is not underlined, and because at claim 19, line 3, the word "organic" is both underlined and struckthrough. Any future amendments should be carefully checked to ensure compliance with the amendment rules.

4. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis in the claims for the phrase "said organ transplantation" at claim 21, line 1. It is believed that claim 21 should instead depend upon claim 7.

5. Claim 19 is objected to because of the following informalities: At claim 19, line 2, "methotrexate" (second occurrence) is misspelled. At claim 19, line 3, the comma after "1:10" should be deleted. Appropriate correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 10, 12-14, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the prevention of transplantation-associated immune responses, does not reasonably provide enablement for the treatment of transplantation-

associated immune responses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. With respect to (1), the nature of the invention is the modulation of transplantation-associated immune responses. As described at page 6, lines 10-32, of the specification, "modulation" includes the prevention and the treatment of such responses. With respect to (2), the Wolff et al abstract teaches that conjugates identical to the ones claimed by Applicant are capable of preventing acute graft versus host diseases (GVHD), but are not capable of treating GVHD. With respect to (3), the relative skill of those in the art is high. With respect to (4), the therapeutic arts in general are unpredictable. With respect to (5), the claims are relatively broad with respect to the cytostatic or immunosuppressant carboxylic group-containing organic compound to be used in the conjugates. Any cytostatic or immunosuppressant is embraced within the scope of the claims as long as it comprises a carboxylic acid group. As noted above, the claims embrace both the prevention and the treatment of transplantation-associated immune responses. With respect to (6) and (7), Applicant does not provide any specific guidance in the specification as to how the conjugates can be used

to treat transplantation-associated immune responses. The disclosure in the specification concerning administration steps (see page 6, line 37 - page 7, line 20) is a recitation of generic administration steps and dosages, which does not distinguish over the administration steps and dosages in the Wolff et al abstract's failed experiments. The only working example disclosed in the specification (Example 2) concerns the prevention of transplantation-associated immune responses. There are no examples, in vivo or in vitro or otherwise, directed to treating transplantation-associated immune responses. With respect to (8), in view of the failure in the art to be able to treat transplantation-associated immune responses, and the lack of any disclosure in the specification as to how the prior art failures can be avoided, the quantity of experimentation necessary to practice this part of the invention would be vast. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1, 3-8, 10, and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by the Wolff et al abstract (Blood, Vol. 102, No. 11, page 404b). The Wolff et al abstract teaches the use of methotrexate-human serum albumin and aminopterin-human serum albumin conjugates to prevent, although not to treat, experimental acute GVHD in rats who have undergone bone marrow transplantation. Bone marrow cells and spleen T-cells are transplanted from other rats, i.e. are allogeneic transplants. Note that Applicant defines "modulating" at page 6, lines 10-27, of the specification as including prevention of transplantation-associated immune response. With respect to instant claim 5, because the Wolff et al abstract teaches administering

the same active agents according to the same method steps to the same subjects as are claimed by Applicant, inherently chronic GVHD will be prevented in the method of the Wolf et al abstract to the same extent claimed by Applicant. Sufficient evidence of similarity is deemed to be present between the method of the Wolff et al abstract and Applicant's claimed method to shift the burden to Applicant to provide evidence that the claimed method is unobviously different than that of the Wolff et al abstract. With respect to instant claim 7, bone marrow is an organ.

9. Claims 15, 17, 18, and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Sutton et al (U.S. Patent No. 5,993,805) in view of the European Patent Application 0 282 057 or Low et al (U.S. Patent No. 5,688,488). Sutton et al teach adding EDCI to a solution of methotrexate, stirring to ensure initiation and complete activation of the methotrexate, and then adding HSA, whereby the methotrexate is bound to amine residues on the HSA. See, e.g., Example 12. Sutton et al teach reacting methotrexate with EDCI in solution, but do not specify the solvent. The European Patent Application '057 teaches activating methotrexate with EDCI for reacting with an antibody carrier, wherein the activation reaction is carried out in dry DMF. Low et al teach that folic acid (of which methotrexate is an analog) can be activated by EDC in a DMSO solution. The activated folic acid is then reacted with a protein, ribonuclease. See, e.g., column 18, lines 47-50. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to perform the activation reaction of Sutton et al using the dry DMF solvent of the European Patent Application '057 or the DMSO solvent of Low et al, because the European Patent Application '057 teaches that dry DMF is a known solvent for performing the activation reaction of Sutton et al, because Low et al teach that DMSO is a known solvent for performing the activation reaction of a compound analogous to methotrexate,

and because substitution of one known reaction solvent for another with only the expected result that methotrexate is activated by EDCI is prima facie obvious. With respect to the "activated by heating" step recited in claim 20, the claim does not specify any particular degree of heating. However, Applicant's specification at page 8, lines 36-37, states that activation can occur at temperatures ranging from 10°C to 100°C, which embraces room temperatures. Sutton et al do not disclose a temperature for their step of reacting methotrexate with EDCI, and therefore it is presumed to occur at room temperature and satisfies Applicant's claim limitation. In any event, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal temperatures for Sutton et al's step of reacting methotrexate with EDCI, because reaction temperature is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts.

10. Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being obvious over Sutton et al (U.S. Patent No. 5,993,805) in view of the European Patent Application 0 282 057 or Low et al (U.S. Patent No. 5,688,488). Application of the references is the same as in the above rejection of claims 15, 17, 18, and 20. Sutton et al do not teach a molar ratio of methotrexate and albumin reactants of from 10:1 to 1:10, or of from 1.5:1 to 1:1.5. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal molar ratios for the methotrexate and albumin reactants of Sutton et al, because reactant ratio is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts.

11. Applicant's arguments filed November 3, 2008 have been fully considered but they are not persuasive.

Applicant's method of synthesis claims continue to be rejected based upon Sutton et al (U.S. Patent No. 5,993,805) in view of the European Patent Application 0 282 057 or Low et al (U.S. Patent No. 5,688,488). In the previous set of claims, dependent claim 20 specified that an organic solvent was used as the reaction medium for the activation of the carboxyl group-containing compound, and this claim limitation was addressed by a combination of references applied under 35 U.S.C. 103. With Applicant's amendment, this limitation has now been shifted into the independent claim. However, Applicant's only traversal is that Sutton et al do not teach or suggest the use of an organic solvent as the reaction medium. This argument is unconvincing because the synthesis claims continue to be rejected over the same combination of references applied in the previous Office action against claim 20. It is not relevant to an obviousness rejection based upon a combination of references that any single reference does not teach or suggest a claim limitation.

12. Rameshwar (U.S. Patent Application Publication 2003/0225010) is cited as art of interest, teaching that bone marrow is an organ. See paragraph [0028].

The Vallera et al article (Blood, Vol. 88, pages 2342-2353) and the Wolff et al abstract (Blood, Vol. 102, No. 11, page 404b) are re-cited in the attached Notice of References Cited (PTO-892) in order to provide publication dates with their citations.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/
Primary Examiner, Art Unit 1654

JRussel
January 1, 2009